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(54) Title: NUTRITIOUS FOOD PREPARATIONS AND METHODS FOR MAKING THEM			
(57) Abstract  Methods for producing a roasted soybean, and soybeans prepared by the methods, are disclosed. Synergistic food preparations useful for the treatment or prevention of disease are also disclosed. The synergistic food preparations can include the roasted soybeans of the invention.			

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**NUTRITIOUS FOOD PREPARATIONS AND**  
**METHODS FOR MAKING THEM**

*Background of the Invention*

5 Soybeans are a source of fiber and of nutrients including protein, Vitamin E, fats, isoflavones, and other micronutrients. However, raw soybeans have a hard texture and a somewhat unpleasant flavor and must generally be cooked to soften the bean and remove the unacceptable "beany" taste. Soybeans are commonly cooked by frying in oil or other fats; the resulting product has an acceptable taste, but the fat content is generally quite high, with the consequence that oil-roasted soybeans are high in calories, with a high percentage of calories from fat. In addition, soybeans roasted according to conventional methods often have a limited shelf-life, and for longer storage may require special packaging to prevent rancidity.

15 *Summary of the Invention*

In one aspect, the invention provides a method for producing a delicious edible roasted soybean without deep-fat frying. The subject method provides an advantage over conventional oil-roasting processing methods in that the basic low-fat nature of the soy bean (preferably less than about 20% fat vs. 50+% found in oil-roasted soybeans or in fatty nuts) is retained. Thus, the invention provides a roasted soybean that can be utilized in foods as a substitute for high fat content nuts or legume seeds used as nuts, such as peanuts. In addition the method maintains the integrity of the nutrient ingredients in soybeans that make them valuable for the prevention and treatment of various chronic diseases (such as cardiovascular disease (CVD), cancer, diabetes and osteoporosis, and conditions associated with post menopause such as hot flashes), thus providing a roasted soybean that substantially retains the nutrient value of raw soybeans.

In one embodiment, the invention provides a method for producing a roasted soybean. The method comprises subjecting a soybean to hot air roasting, the air having a temperature of at least about 570°F for at least about 15 seconds, such that the soybean is roasted. In preferred embodiments, the soybean is not contacted with additional oil or fat. In certain embodiments, the soybean is an unhulled soybean. In certain preferred embodiments, prior to subjecting the soybean to the hot air, the soybean is soaked in water or sprayed with water.

In another embodiment, the invention provides a roasted soybean produced by the methods of the invention.

- 2 -

In another aspect, the invention provides a food product comprising nutrients or compounds selected for the treatment of a pre-selected disease condition or conditions. Thus, the invention provides healthy food or nutraceutical ingredients which can be used in the prevention and treatment of various diseases, such as cardiovascular disease, cancer, osteoporosis and diabetes, and post-menopausal symptoms such as hot flashes and can be applied to certain (CVD) high risk populations such as those who show high density lipoprotein cholesterol (HDL) levels. In a preferred embodiment, the food product comprises the roasted soybean or soybean compositions of the invention. In addition to containing the roasted soybean, these formulations can include synergistic nutrients to influence metabolic processes in which the nutrient activity of the food product is greater than the sum of its parts.

#### Detailed Description of the Invention

This invention relates to synergistic food products, to roasted soybeans useful in synergistic food products, and to methods for producing roasted soybeans.

#### I. Methods for Roasting Soybeans

In one aspect, the invention provides a method of processing soybeans which (1) produces toasted, whole soybeans having an acceptably soft nut-like texture and roasted flavor without deep-fat frying, and (2) retains ingredients such as genistein and vitamin E which are beneficial in the prevention and control of diseases such as cardiovascular disease, osteoporosis, diabetes and cancer. Previously, roasted soybeans were often produced by deep-fat frying, which can leave them with a high oil and calorie content similar to conventional nut meat products.

Raw soybeans possess a hard, unacceptable texture for direct consumption. If an acceptable texture and flavor can be created in soybeans, for example by roasting, they can be utilized as a delicious ingredient in reduced calorie foods, or eaten as an alternative to peanuts and other high fat content snack foods. Furthermore, it is preferable that such a process retain substantially intact the nutrient constituents of soybeans which are known to have an impact on the prevention and control of cardiovascular disease, osteoporosis, diabetes, conditions associated with pre- and post-menopause, and cancer.

In one aspect, the invention provides a method for producing a dry-roasted (or toasted) soybean. According to one embodiment of the subject method, soybeans are air-roasted at a temperature of at least about 380°F, more preferably at least about 450°F, more preferably at least about 500°F, still more preferably at least about 550°F, more

preferably at least about 570°F, more preferably at least about 580°F, and more preferably at least about 600°F. The roasting temperature is preferably not greater than about 630°F, more preferably not greater than about 620°F. The time required for roasting to be complete will vary depending upon the size of the soybeans, whether the beans are whole or split, and on the moisture content of the raw beans, e.g., due to optional pre-soaking. In general, the soybeans are roasted until the soybeans have a crisp texture and a water content of between about 4% to 12%. According to the invention, the soybeans are exposed to hot air at a temperature in the range of about 570°F to about 630°F for a period of not more than about two minutes, more preferably not more than about 1.5 minutes, such that the soybeans are roasted. In certain preferred embodiments, the roasting time is not more than about one minute, or not more than about 30 seconds. In embodiments in which a lower roasting temperature for example, about 450°F) is employed, the roasting time will in general be longer than when higher temperatures (e.g., about 580°F) are employed. If the beans are soaked in water or brine prior to roasting, the roasting time will generally be longer than where the beans are not pre-soaked. Thus, for example, pre-soaked beans can be roasted at a temperature of about 450°F to 500°F for about 4 to 10 minutes to provide a crisp toasted soybean. In certain preferred embodiments, the soybeans are not contacted with fat or oil prior to and/or during the roasting process. Soybeans roasted according to the subject method preferably have a light brown color and a nut-like taste.

In general, it is preferable to use food quality soybeans in the methods of the invention (see, e.g., K. Liu *et al*, INFORM 6:595 (1995)). Food-grade soybeans are generally characterized by bulk characteristics: > 95% whole beans, <2000 beans / lb., each bean with a clear or white hilum. For use in the present invention, the beans can be whole or split, hulled or dehulled. Advantageously, the soybeans need not be dehulled prior to roasting (the hulls are edible after roasting), thus simplifying the roasting process and increasing the throughput of the process. Food-grade soybeans are especially preferred when the beans are not soaked in water prior to roasting, as described below. Food-grade soybeans also can generally provide a larger, more flavorful toasted product than smaller inferior grade soybeans. Furthermore, it has now been found that toasting of soybeans, particularly without added water, can occasionally result in a hard, unacceptable product (e.g., a few soybeans of a batch of roasted beans may be hard or have an undesirable appearance); food-grade soybeans are less likely to produce such an unacceptable product.

Prior to roasting, soybeans can be soaked in water or salt brine, if desired. However, in a particularly preferred embodiment, the soybeans are not soaked in water

prior to roasting. The soaking step, if used, can result in a crisper roasted product, and is preferred when the soybeans are small or of inferior quality. As an alternative to soaking, the raw soybeans can be sprayed with water prior to roasting. The water (for soaking or spraying) can include flavors, colors, and the like, if desired, to improve the properties of the roasted soybeans. For example, salt water can be used in the soaking step if a salted soybean is desired. If the soaking step is employed, the beans can be soaked for about 15 to 30 minutes. The beans can be soaked until some swelling has occurred. The soaking process is preferably performed at a temperature between about 50°F and about 120°F, preferably between about 60°F and about 80°F. Longer soaking times, and/or higher temperatures, can be employed. After soaking, the excess water is drained and the wet beans are permitted to stand (to temper) for about 30 to 60 minutes. The tempering step permits the water to become distributed throughout the bean, although the distribution may not be uniform. The tempered beans are dried and roasted at high temperatures as described herein to a final moisture content of about 4 to 12% water.

Any means for roasting the soybeans can be employed, including ovens useful for the roasting of other beans or nuts. A particularly preferred oven is an impingement or "fluidized-bed" forced convection oven. In preferred embodiments, the soybeans are roasted in a continuous, rather than batch, process, to maximize throughput of roasted beans. In certain embodiments, it is preferred to use a steam toasting process, as with a puffing gun. In certain preferred embodiments, the soybeans are roasted by contacting the beans with hot air, although other hot gases (e.g., carbon dioxide or nitrogen gas) can be employed. As used herein, the term "hot air" can refer to hot gases which include water vapor, e.g., in a steam toasting process.

After roasting the soybeans can be flavored, colored, or processed as is conventional in the art. Furthermore, the soybeans can be used in a substantially whole form, or can be crushed, split, milled, or otherwise prepared for use in food products.

It has been found that soybeans roasted according to the invention have excellent keeping qualities, e.g., have an unexpectedly long shelf-life, while also having good flavor and texture comparable to beans processed according to conventional methods. In contrast to soybeans prepared by certain prior known methods, soybeans roasted according to the invention can, in some embodiments, be stored at room temperature (without special storage conditions such as vacuum sealing or flushing with inert gases such as nitrogen) for periods of up to one year, or in some cases even longer, without significant spoilage and/or oxidation, and the attendant development of off-flavors and other undesirable qualities.

## II. Roasted Soybeans

In another aspect, the invention provides a roasted soybean product, which, in certain embodiments, can be produced according to the methods of the invention. In preferred embodiments, the roasted soybeans of the invention retain at least about 50%, more preferably at least about 80%, most preferably at least 95%, of at least one selected nutrient present in unroasted soybeans (e.g., on a weight/weight basis). For example, as described in more detail below, raw soybeans contain antioxidant and anti-cancer isoflavones. In a preferred embodiment, soybeans roasted according to the invention retain at least about 50%, more preferably at least about 80% of the isoflavones present in the raw soybean. The selected nutrient, e.g., isoflavones, is preferably present in the roasted soybean in active form, i.e., is not degraded or inactivated by the roasting process.

The roasted soybean of the invention preferably has a moisture content of between about 4% and about 12%, a fat (oil) content of not more than about 25%, more preferably not more than about 20%, most preferably not more than 18% oil by weight, has a light brown or tan color, has a crisp texture, and, if roasted without dehulling, has an edible hull. The soybeans of the invention have a delicious nut-like flavor, and preferably have substantially no beany flavor. As noted above, the soybeans of the invention are also characterized in that they have excellent keeping qualities, e.g., long shelf-life.

The invention also provides food products comprising soybeans roasted according to the methods of the invention. For example, the invention contemplates food products which include whole or crushed roasted soybeans, soybean flour, oil, or milk, soy protein concentrate, and other products made by processing soybeans which have been roasted according to the methods described herein. Examples of certain food products which can include the roasted soybean of the invention are described below. In certain preferred embodiments, such food products comprises at least about 10% by weight of the roasted soybeans of the invention, more preferably at least about 25%, 50%, 75%, or 90% by weight of the roasted soybeans of the invention. However, in certain embodiments, such food products comprise not more than about 90% by weight of the roasted soybeans of the invention, more preferably not more than about 75%, 50%, 25%, or 10% by weight of the roasted soybeans of the invention. It will be understood that such food products can contain binders, emulsifiers, flavors, humectants, stabilizers, preservatives, and the like, such as are conventional in the art. In certain

embodiments, it is preferred that the soybean of the invention is used whole or split in a food product.

The inventive roasting method transforms the raw soybean into a highly palatable bean that can be used, e.g., as a delicious "nut" in many applications where, for example, peanuts are currently being used. Because of the low cost of soybeans and of the inventive roasting process, roasted soybeans can be an economically attractive alternative to roasted nuts. In addition, because of their relatively low fat content, relatively high protein content, and desirable texture and flavor, the toasted soybeans may be used for direct consumption (even eating out of hand), as a relatively low-fat nut substitute (20% vs. 50+% in fatty nuts), in snacks, used whole, split, broken or ground to various sized pieces or particles for confectionery or bakery applications or as an alternative to nut meat products.

Because of its richness in "nutraceuticals" (e.g., phytohormones such as phytoestrogens, fiber, anti-oxidants, etc.), the toasted soybean of the invention can be utilized in products and formulations specifically designed as health foods which prevent, treat, or control such diseases as cardiovascular disease, osteoporosis, diabetes and cancer and post-menopausal symptoms such as hot flashes.

There are at least nine ingredients found in the dehulled soybean with reported health benefits such as cholesterol lowering properties: lecithin, soybean oil, steryl glycosides, soy flour, soy protein concentrate (water-washed), isolated soy protein, soy fiber, saponins, and isoflavones.

Soy flour, water-washed soy protein concentrate and soy protein isolate are rich sources of soybean isoflavones (See Example and Table 10). These isoflavones from soybeans have been shown to be health protectants. They are cholesterol-lowering agents (1) and also possess anti-carcinogenic (2), anti-thrombotic (3), and antioxidant activities (4). Furthermore, genistin and diadzin and their aglycones, genistein and diadzein, which are the major isoflavones in soybeans (5), are estrogen analogs.

Examples of food formulations of the invention which can be used for the treatment or prevention of certain conditions are described below.

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### III. Synergistic Food Compositions

In another aspect, the invention provides food compositions useful for the prevention of or treatment of disease conditions in humans or animals. In general, the subject food compositions comprise at least two synergistic ingredients or elements, i.e., ingredients which, when administered together, provide a benefit (e.g., a biological

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effect, e.g., in disease prevention or treatment) which is greater than the sum of the benefits that would be attained if the ingredients were administered separately.

Thus, for example, ingredients which are useful for the treatment or prevention of disease may (although they need not) act synergistically when administered to a  
5 subject (i.e., a human or animal).

In certain embodiments, the synergistic food compositions of the invention comprise soybean or a soybean component, e.g., whole beans, split, or crushed soybeans, soybean oil, soy flour, soybean curd (tofu), and the like. In certain embodiments, the invention contemplates the use of extracts of soybeans, e.g., extracts containing partially  
10 or wholly purified nutrients from soybeans. In preferred embodiments, however, a "whole" soy product is preferred, i.e., a soy product which is derived from the whole bean and is not an extract thereof. In a most preferred embodiment, the soybean used (either the bean itself or an extract thereof) is a roasted soybean of the invention, e.g., a soybean roasted according to the methods of the invention.

15 The food compositions of the invention preferably comprise only whole foods, i.e., do not include supplements as a source of a therapeutically-effective compound or component. The language "exogenous" therapeutically-effective component, as used herein, refers to a therapeutically-effective component in an isolated or purified form that is added as a supplement to a food product. Accordingly, in preferred embodiments,  
20 the synergistic food compositions of the invention are substantially free of exogenous therapeutically-effective components, i.e., are substantially free of extracts (or otherwise purified or chemically synthesized) therapeutically-effective components. In particularly preferred embodiments, all of the components (e.g., food components) included in a food composition of the invention are classified as "Generally Recognized As Safe"  
25 (GRAS) by the Food and Drug Administration.

Certain non-limiting examples of disease conditions which can be treated with synergistic food compositions of the invention are described below.

#### (a) Cardiovascular disease

30 There have been several studies of the cholesterol-lowering properties of soybean oil when replacing saturated vegetable oils or animal fat (6). The mechanism of action for cholesterol-lowering by polyunsaturated vegetable oils, such as soybean oil, appears to be the upregulation of the LDL receptor (7).

Soybean oil and the toasted soybean of the invention (as described above) are  
35 also sources of the anti-oxidant, Vitamin E. (see Example and Table 9) Vitamin E ingestion in animals and both epidemiological and intervention studies in humans have

demonstrated reductions in atherosclerosis and mortality resulting from cardiovascular disease (8,9).

Studies also support the cholesterol-lowering properties of soybean lecithin (10-12). While there has been some controversy as to whether the lecithin effect goes  
5 beyond its linoleate content, our own cholesterol-lowering and atherosclerosis studies in animals (unpublished observations) would support this view. In addition, more recent studies in animals (13), suggest that the cholesterol-lowering properties of steryl glycosides isolated from soybeans are associated with enhanced fecal cholesterol excretion.

10 There have been several animal and human studies using both soy protein concentrate and isolate which have demonstrated significant cholesterol-lowering properties (14,15). In addition, soybean polysaccharides containing 74% soy fiber have recently been reported also to have cholesterol-lowering properties (16). Soy protein concentrates are also a source of saponins, which independently have cholesterol-  
15 lowering (17) and anti-carcinogenic properties (18). Soy flour also lowers blood cholesterol and reduces atherosclerosis in rabbits (19).

Soybean intake and genistein intake may reduce the thrombotic events associated with atherosclerosis. Genistein prevents thromboxane  $A_2$  - and collagen-induced platelet activation as well as ADP-induced activation of platelets in vitro. Blockage of  
20 tyrosine kinase activity by genistein also prevents thrombin-induced platelet activation and aggregation in vitro. It is reasonable to believe, therefore, that genistein can reduce the deposition and aggregation of platelets at sites of arterial injury associated with atherosclerotic development. Because platelet-derived growth factor is released by activated platelets during the formation of the thrombus, genistein would have the  
25 additional benefit of acting as an inhibitor of the activity of this growth factor (20).

#### (b) Hormonal cancer risk and osteoporosis risk

Genistin and diadzin and their aglycones are the major isoflavones in soybeans (21). These isoflavones are structural estrogenic analogs which satisfy estrogen's bone  
30 maintenance capabilities without having the hormonal side-effects associated with estrogen administration in the mitigation of osteoporosis. One of the estrogen side-effects is the increase in ovarian cancer risk for some individuals. As a result, the isoflavones will may be effective in reducing hormonal risks of osteoporosis and cancer (especially important in post-menopausal women).

35 Feeding a 30% soybean diet has been shown to protect mouse liver from nitrosamine-induced cancer. Rats consuming a soy-based diet developed 50% fewer

mammary tumors in a N-methyl-N-nitrosurea (NMU) model of breast cancer. These experiments showed a 50% reduction in experimentally induced X-ray irradiated mammary tumors in rats consuming a powdered soybean diet. (5) Barnes *et al.* (5) showed that soybean ingestion led to a reduction in mammary tumor growth in both the  
5 NMU and the DMBA rat models of breast cancer. In these models, tumor formation was negatively correlated with total dietary isoflavone concentration and, in particular with dietary intake of genistein and urinary isoflavone excretion level. In addition, the results from a follow up study found that a soybean product from which the isoflavone had been chemically removed had no effect on mammary carcinogenesis (1).

10 Three epidemiological trials have reported a protective effect of soybean against the development of breast cancer. In two prospective trials, an inverse relationship was found between intake of miso soup or tofu, and subsequent risk of breast cancer, while it was also shown that a high intake of miso soup reduced the subsequent risk in Japanese women. A recent case-control study found a significant inverse association in pre-  
15 menopausal women between breast cancer risk and soybean protein intake. Genistein has also been shown to inhibit tyrosine protein kinases and to block angiogenesis which are also proposed mechanisms of anti-carcinogenesis.(3)

Soybean protein also prevents bone loss in an ovariectomized rat model of osteoporosis (22).

20 The effectiveness of the treatment and prevention of certain conditions or disease indications can be significantly increased by utilizing interventions which include functional foods (e.g., nutraceuticals) and/or ingredients with biological activities that act synergistically, so that the whole is more efficacious than the composites. For example, hypercholesterolemia is an established risk factor for cardiovascular disease  
25 (CVD). Elevated blood cholesterol levels and, in particular, low density lipoprotein (LDL) cholesterol levels are the result of several mechanistic abnormalities which include alteration in (a) cholesterol absorption, (b) cholesterol synthesis (c) cholesterol excretion (d) bile acid metabolism and (e) LDL receptor activity. This raises the possibility that the efficacy for the treatment of hypercholesterolemia can be increased if  
30 one develops a synergistic intervention which would affect at least two or more of these metabolic processes simultaneously, and which, at the same time do not interfere negatively with each other. An example of this synergism is the drug control of cholesterol levels. Cholestyramine or Questran (Bristol-Myers-Squibb) is a non-absorbable resin which binds bile acids, and in the process, enhances fecal excretion of  
35 bile acids, reduces hepatic pools of cholesterol and subsequently blood LDL cholesterol levels. However, the efficacy of this drug is poor, requiring intake of as much as

20g/day to reduce blood cholesterol levels up to 20%. The failure of this approach is explained by the body's natural response to decreasing pools of hepatic cholesterol levels, by the liver synthesizing more cholesterol, and therefore normalizing hepatic cholesterol pools. However, if Questran is combined with a cholesterol-synthesis inhibitor such as Lovastatin (Merck), the degree of blood cholesterol lowering is increased significantly because Lovastatin has reduced the body's natural tendency to increase cholesterol synthesis. The same synergy is found by combining food ingredients as described herein.

In the discussion which follows, nutraceutical formulations are provided for the prevention, treatment, or management of disease conditions. In a general aspect, the nutraceutical formulations of the invention can comprise any food or food-derived materials, provided that the nutrients present in the formulation can act synergistically to prevent, treat, ameliorate, or manage disease conditions. In certain embodiments, the nutraceutical formulations include the toasted soybean composition described above, i.e., a toasted soybean composition produced by the methods described herein. In some embodiments, the nutraceutical formulations include ingredients derived from other foods, and can, in certain embodiments, be substantially soybean-free. The nutraceutical food formulations are preferably constituted so as to meet the FDA food designation. In formulations which include ingredients derived from foods, the formulation preferably meets the FDA food supplement designation. In this case, the activity of the formulation is enriched above the level provided by the unsupplemented food, by adding concentrated food derivatives to a level exceeding that normally found in the foodstuff. The formulations of the invention can thus meet FDA designations whether the food product is supplemented or unsupplemented. It will be understood that the invention contemplates combinations of whole foods and supplements, i.e., food components which are complementary (in a synergistic sense) to the whole food component. In preferred embodiments, the food formulation includes only whole foods.

#### Formulations which regulate cholesterol

There is little controversy regarding the importance of hypercholesterolemia as a risk factor for cardiovascular disease (CVD). A recent fact sheet of the American Heart Association (AHA) indicates that, at least 30% of Americans have blood cholesterol levels greater than or equal to 240 mg/dL, placing them in a high risk category for CVD. Most health professionals and health agencies have also realized the importance of knowing which lipoprotein fraction is carrying the majority of an individual's circulating cholesterol. Blood cholesterol levels in males are transported predominantly in a

lipoprotein fraction called low density lipoprotein (LDL), and it is elevations of this particular lipoprotein which are associated with increased risk of CVD. The exact mechanism(s) for this disease association are not well understood, although (a) the ability of LDL to deposit cholesterol into cells that comprise blood vessel walls such as coronary arteries and (b) susceptibility of LDL to oxidative stress thereby increasing the ability of this lipoprotein to increase the accumulation cholesterol into arteries are often cited. The other major lipoprotein class which can transport substantial amounts of blood cholesterol, especially in pre-menopausal women is the high density lipoprotein (HDL) fraction. In contrast to LDL, elevated levels of HDL decrease the risk of CVD by mechanisms not well established, although its postulated ability to remove cholesterol from cells which make up the blood vessel walls has often been cited as an explanation for its protective role in CVD. Thus, an individual can be at increased risk for development of CVD as a result of both elevated LDL and/or reduced HDL, and both are included as significant and independent risk factors for CVD in the recently-published report of the second Adult Treatment Panel (ATPII) of the National Cholesterol Education Program.

Therefore, it is most desirable that any recommended diet and/or drug intervention designed to lower one's blood cholesterol levels would do so by reducing LDL cholesterol levels, exclusively, without decreasing the beneficial HDL fraction. However, the diet interventions recommended by most health agencies such as the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) and the American Heart Association (AHA) often fall short of this objective because they focus their attention on modifying the levels of dietary fat and cholesterol and, the type of fatty acids for the prevention and treatment of hypercholesterolemia. For example, a recently-completed NIH sponsored study of dietary intervention for the treatment of hypercholesterolemic individuals revealed that consumption of a modified AHA Step II diet (< 25% Kcals as total fat, < 200 mg dietary cholesterol/day and < 7% saturated fatty acids resulted in a reduction in plasma total cholesterol of only 5-10% and, in addition, for many individuals, HDL cholesterol was reduced as much, if not more than LDL cholesterol. Thus, for many individuals, these diet interventions will not lower blood cholesterol levels sufficiently enough to not require drug interventions, but even more importantly, by reducing the beneficial HDL as much or more than the detrimental LDL, the all-important lipoprotein profile (LDL/HDL ratio) is not improved.

Thus, identification and evaluation of alternative dietary interventions which predominantly reduce LDL cholesterol without an accompanying effect on HDL could be a major advancement in the prevention and treatment of hypercholesterolemia and the

resultant CVD. For example, soluble fibers, vegetable proteins with and without isoflavones, soybean lecithin and unsaponifiables such as plant sterols, to name a few, are all food components with reported cholesterol lowering properties, in both animals and humans. The magnitude of the cholesterol-lowering effect with these interventions in hypercholesterolemic individuals often-times exceeds the traditional interventions. Although the effects of such interventions on a variety of chronic diseases continue to be investigated with a good deal of success, there has been little effort in adopting them into mainstream thinking for the treatment of hypercholesterolemia. In addition, there has been little effort in incorporating these interventions into functional foods or nutraceuticals.

Water soluble fibers can lower blood cholesterol levels, and in particular LDL cholesterol up to 20% without reducing the beneficial HDL cholesterol. Thus, guar gum, pectin, psyllium, oat bran, soy fiber and konjac fiber (23) can reduce blood cholesterol levels by mechanisms which include binding and excretion of bile acids, products of cholesterol metabolism and inhibition of cholesterol synthesis by short chain fatty acids produced by gut bacterial fermentation.

Vegetable protein and in particular, soy protein, when replacing animal protein in the diet can also lower LDL cholesterol levels up to 20% without reducing HDL cholesterol levels. (6) Although there remains some uncertainties, proposed mechanism(s) of action of soy protein include (a) inhibition of dietary cholesterol absorption (b) increased fecal sterol excretion and (c) up-regulation of the LDL receptor.

Unsaponifiables from vegetables, fruits and oils, such as plant sterols can lower blood cholesterol levels. Specifically beta sitosterol, sitostanol and oryzanol, a ferulate ester of triterpene alcohol can lower LDL cholesterol without reducing HDL cholesterol. These unsaponifiables inhibit the absorption of dietary cholesterol. Another group of unsaponifiables are tocotrienols, analogs of tocopherol which inhibit cholesterol biosynthesis.

Soybean lecithin can also lower LDL cholesterol levels without reducing HDL cholesterol (10-12). While its mechanism of action is uncertain, the linoleate component of lecithin upregulates the LDL receptor.

Calcium can also lower LDL cholesterol without reducing HDL cholesterol levels (25). One of its mechanisms of action is the binding of cholesterol-raising saturated fatty acids, preventing their absorption into the blood stream.

Conjugated linoleic acid (CLA), an isomer of linoleic acid, also lowers LDL cholesterol levels without reducing HDL cholesterol (26) by mechanisms which remain to be elucidated.

An illustrative cholesterol-lowering formulation, which includes nutrients which act synergistically via different mechanisms, is shown in Table 1, below. Such a formulation can include functional foods such as the toasted soybean of the invention (containing soy protein and genistein--upregulates LDL receptor activity), oat fiber (binds bile acids) and rice bran oil or corn fiber oil (rich in unsaponifiables which inhibit cholesterol absorption and cholesterol synthesis. Consumption of oat fiber and corn fiber oil or rice bran oil would enhance fecal bile and cholesterol excretion, respectively. The unsaponifiable fraction of rice bran oil (tocotrienols), a cholesterol synthesis inhibitor, will blunt the body's natural tendency to increase cholesterol synthesis. These two actions will normally increase hepatic LDL receptor activity, thus reducing LDL levels. However, both the soy protein and the isoflavone genistein components will further increase LDL receptor activity further reducing LDL levels.

Table 1

Cholesterol-lowering formulation

Synergistic Function	Decreased Cholesterol Absorption	Increased Fecal Bile Acids	Increased Fecal Cholesterol Excretion	Decreased Cholesterol Synthesis	Increased LDL receptor activity	Binds fatty acids
<b><u>Foods</u></b>						
Soy protein	X				X	
Oat fiber		X				
Soybean oil	X		X		X	
Rice bran oil	X		X	X		
Corn fiber oil	X					
<b><u>Ingredients</u></b>						
Sitosterol or Sitostanol	X		X			
Oryzanol	X		X			
Tocotrienols				X		
Calcium	X					X
Lecithin			X			
Saponins	X		X			
Genistein					X	

Thus, in one embodiment, the invention provides a cholesterol-lowering synergistic food formulation which comprises at least two components selected from the group consisting of soy protein, oat fiber, soybean oil, rice bran oil, and corn fiber oil.

5 In addition to a formulation based on the synergy of functional foods, the invention provides formulations based on the synergy of individual active ingredients or supplements (see Table 1). Thus, one of many synergistic formulations based on active ingredients could include sitostanol (1-2g/day) or oryzanol (300mg/day) to decrease dietary cholesterol absorption, tocotrienols (300mg/day), and lecithin (9g/day) to  
10 decrease cholesterol synthesis and genistein (50mg/day) to increase LDL receptor activity.

#### Water and Lipid Soluble Anti-oxidants

There are several studies which suggest that a combination of water soluble anti-oxidants (e.g., ascorbic acid) and lipid soluble anti-oxidants (e.g., tocopherol) have better  
15 anti-oxidant activity than either alone. For example, the addition of the water-soluble antioxidant, ascorbic acid, maintains higher blood level of the lipid-soluble antioxidant by enhancing the regeneration of the latter. However, in addition to these more common anti-oxidants are those water-soluble anti-oxidants found in green (catechins) and black  
20 (theaflavins) tea which are several fold greater in activity than ascorbate or tocopherol. Genistein (see above), a soy protein isoflavone, has also been found to be a potent anti-oxidant. (4)

An exemplary synergistic formulation for anti-oxidant activity based on functional foods or beverages (Table 2) could include (a) toasted soybeans, which are  
25 rich in tocopherol, a fat soluble anti-oxidant; and the soy protein component of the toasted soybean, rich in the isoflavone genistein, a water soluble anti-oxidant, (b) rice bran oil, rich in oryzanol whose ferulate component is an anti-oxidant; and (c) tea, rich in polyphenols which are also anti-oxidants.



Table 2  
Anti-oxidant formulation

Synergistic Function	Fat Soluble Anti-oxidant	Water Soluble Anti-oxidant
Foods/beverages		
Soybean oil	X	
rice bran oil	X	X
Soy protein		X
Tea		X
Ingredients		
Tocopherol	X	
Tocotrienols	X	
Oryzanol		X
Genistein		X
Catechins/Theaflavins		X
CLA	X	

5

An exemplary synergistic formulation based on active ingredients or supplements (Table 2) includes (a) tocopherol, a fat-soluble anti-oxidant (b) genistein, a water soluble anti-oxidant from soy protein (c) the ferulate component of oryzanol, an anti-oxidant from rice bran oil and (d) the catechins and theaflavins, water soluble anti-oxidants from tea.

10

#### Formulations which regulate clotting

Besides elevated blood cholesterol, thrombus or clot formation as a result of abnormal activity of various clotting factors and platelet aggregation contributes to CVD. While one of the most common treatments to reduce the tendency to clot and platelets to aggregate is aspirin, there are several nutrients which also could be used for this purpose. For example, fish oil supplements such as EPA and DHA can beneficially alter the homeostasis system. There is evidence that soybean isoflavones such as genistein can beneficially influence thrombus formation. (3) Both tocotrienols and tea catechins have been shown to reduce platelet aggregation.

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- 16 -

Examples of synergistic formulations that regulate clotting:

Table 3  
Anti-clotting formulation

5

Synergistic Function	Clotting Inhibition	Platelet Aggregation Inhibition	Anti-arrhythmia
Food Beverage			
Fish oil	X		
Flaxseed oil	X		
Rice bran oil		X	
Soy protein	X		
Tea		X	
Ingredients			
Alpha linolenic Acid			
EPA/DHA	X		
Tocotrienols		X	
Genistein	X		
Catechins		X	
CLA			X

10 Fish oil and flaxseed oil can reduce the activity of clotting factor VII and Factor X. Rice bran oil and tea can decrease platelet aggregation. Soybean protein (e.g., of the toasted soybean of the invention) can reduce thrombus or clot formation. EPA/DHA or alpha linolenic acid can reduce clotting factors VII and X. Tocotrienols and tea catechins can decrease platelet aggregation. Genistein can reduce thrombus or clot formation. Accordingly, the invention provides an anti-clotting synergistic food formulation which comprises at least two components selected from the group consisting of soy protein, fish oil, flaxseed oil, rice bran oil, and tea.

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- 17 -

Formulations which regulate cholesterol, clotting, and oxidation

The following is an example of a combined synergistic food and food derivative formulation that regulate a number of factors in cardiovascular disease:

- 5           38 g toasted soybean  
             1.0 g calcium citrate  
             0.3 g oryzanol or 1.5 g sitostanol  
             0.3 g tocotrienols  
             0.5 g EPA/DHA  
 10          1.0 g CLA  
             0.1 g tocopherol  
             3.0 g konnjac fiber

Formulations for Hypertension

- 15           Lowering salt intake is the recommended dietary modification often associated with reduction in hypertension. However, other nutrient interactions which could be used in the prevention and treatment of hypertension include calcium, EPA/DHA, linoleic acid vegetable protein, and high potassium. Thus, an exemplary formulation of the invention includes the toasted soybean of the invention (high in potassium) and/or
- 20           calcium, soy protein, soy lecithin (high in linoleic acid). An exemplary formulation for treatment or prevention of hypertension is shown below in Table 4.

Table 4Formulation for Hypertension

Synergistic Function	Reduced blood flow	Vaso-dilator	Decrease peripheral resistance
<b>Food Formulation</b>			
Fish oil	X	X	X
Milk		?	
Soybean oil		X	
<b>Ingredients</b>			
EPA/DHA	X	X	X
Calcium		?	
Linoleic acid		X	
Lecithin		X	
Potassium		?	

### Formulations for Post-Menopausal Osteoporosis

There are numerous animal and human studies demonstrating the efficacy of calcium for the treatment and prevention of osteoporosis. A recent NIH Consensus Development Conference suggests that women should consume up to 1500mg calcium/day to prevent osteoporosis. They also suggested that women consume at least 800 IU of vitamin D.

Recent studies on women demonstrated that magnesium supplementation (575mg/day) was associated with increased bone density of both the spine and femur.

Animal studies suggest that dietary phosphopeptides prevent bone loss in ovariectomized rats. Thus an exemplary synergistic formulation of the invention for treatment or prevention of osteoporosis includes the toasted soybean of the invention, calcium, magnesium, vitamin D and calcium phosphopeptides. In addition, soy protein enriched in isoflavones and phytoestrogens (e.g., genistein and diadzein) have been shown to reduce osteoporosis in ovariectomized rat models, probably by their estrogenic activity, and, in certain embodiments, can be included in a formulation of the invention.

### Anti-Cancer Nutrient Synergy Formulation

There are several studies which demonstrate that insoluble fibers such as those from fruits, vegetables, wheat and rice reduce the incidence of certain cancers such as colon cancer, possibly by diluting, binding and excreting carcinogens. In addition, the genistein and diadzein isoflavones demonstrate anti-breast cancer activity (3) probably via their anti-oxidant and anti-estrogenic activity. The catechins in tea have been shown to reduce chemically-induced cancers in esophageal cancers in humans (2) probably via their anti-oxidant activity. CLA has been shown to reduce certain cancers (mammary) in various animal models). Thus, an anti-cancer synergy food formulation could include the toasted soybean of the invention and/or a dietary fiber, such as wheat bran, soy protein enriched in isoflavones, tea extract rich in catechins and CLA. An anti-cancer synergistic ingredient formulation could include genistein, catechins, CLA, and saponins.

An exemplary formulation for reducing cancer risk is shown in Table 5.

Table 5  
Formulation for Cancer Risk

Synergistic function	Anti-oxidant	Anti-Mutagenic	Anti-angiogenesis
<u>Food/Beverage</u>			
Toasted Soybean (invention 1)	X	X	X
Rice protein		X	
Soy fiber		X	
Wheat fiber		X	
Tea	X	X	
<u>Ingredients</u>			
Genistein	X	X	X
Catechins	X	X	
CLA	X	X	
Saponins		X	

5

Formulations for Diabetes

There are several studies which suggest that complex carbohydrates such as fibers help maintain blood glucose/insulin homeostasis. More recently, complex polysaccharides from rice may be more efficacious than corn, and resistant starch seems to yield even more efficacy in controlling blood glucose/insulin levels. One animal study with rice protein demonstrated significant efficacy in regulating blood glucose/insulin levels. In addition, since oxidized LDL is more atherogenic than normal LDL, and since the LDL from diabetics is more susceptible to oxidation because their elevated glucose levels modify LDL, an anti-oxidant such as tocopherol should have a beneficial effect in this population.

10  
15

An exemplary formulation for prevention, treatment, or management of diabetes is shown below in Table 6.

Table 6  
Diabetes Formulations

<u>Synergistic Function</u>	<u>Anti-oxidant</u>	<u>Decrease blood glucose + insulin levels</u>
<u>Food formulation</u>		
Toasted soy bean (invention #1)	X	X
Rice fiber		X
Tea	X	
<u>Ingredient formulation</u>		
Genistein	X	
Resistant starch		X
Catechins	X	
Tocopherol	X	

5

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## Exemplification

### Example 1

- 5 Food-grade soybeans (whole, unhulled) were soaked in water for 15 to 30 minutes, and the excess water was then drained off. The beans were allowed to stand for 30 to 60 minutes to temper, and then roasted in an impingement oven for less than 60 seconds (c.g., about 15 seconds) at a temperature of about 600°F. The toasted soybeans had a light brown color, were crisp, and had a pleasant nut-like flavor, without the
- 10 "beany" flavor of raw soybeans. The toasted soybeans were found to be stable in storage for at least one year at ambient temperatures, without significant development of a rancid odor or flavor.

The results of analysis of the toasted soybeans are shown in Table 7.

15

Table 7

Composition of Toasted Soybean Product

<u>Macro Composition</u>	<u>%</u>
Protein	41.0
Oil	20%
Crude Fiber	2.5
Ash	4.5 (w/o salt)
Moisture	5.0

- 20 The results of nutritional analysis of the toasted soybeans are shown below in Table 8.

Table 8

25

Nutritional Analysis of Toasted Soybean Product

	<u>per 100 gm</u>
Calories	410 cal.
Phosphorus	680 mg
Calcium	240 mg
Sodium	70 mg
Potassium	1200 mg

The toasted soybeans were also analyzed for tocopherol levels.

The following methodologies were used: Samples of raw and toasted soybeans was ground finely and treated with hexane containing alpha tocopherol acetate as internal standard. After vortexing, the sample was centrifuged at 2500 rpm. The organic phase was removed and the sample was re-extracted with hexane. The organic phase was evaporated under nitrogen gas and reconstituted with a mobile phase containing acetonitrile/chloroform/isopropanol/water. Alpha tocopherol levels were determined by reverse phase high pressure liquid chromatography (HPLC). The data was expressed as  $\mu\text{g}$  alpha tocopherol per gram dry weight of soybean.

The results are shown below in Table 9, with raw soybean for comparison.

Table 9

Alpha-tocopherol level ( $\mu\text{g/g}$ )	
	Alpha Tocopherol level ( $\mu\text{g/g}$ )
Raw soybean	15.4
Roasted soybean	15.7

It can be seen that there is little difference in the quantities of alpha-tocopherol per gram between raw soybeans and those processed by the method described above.

The isoflavone content of soybeans toasted according to the above method was determined and compared to the isoflavone content of other soybean products. In this experiment, soy ingredients were extracted in organic solvent containing 0.1N HCl and stirred for 2 hrs at room temperature. Extracts were filtered and the filtrate was evaporated. The dried material was re-dissolved in 80% HPLC-grade methanol in water. An aliquot of sample was re-filtered and analyzed by HPLC using a photodiode array detector with authentic diadzein and genistein standards.

The results are shown in Table 10, below. It can be seen that the toasted soybean compares favorably to the raw soybean in the content of two of the three isoflavones tested, and is considerably superior to two common soybean food products, tofu and bean paste in the amounts of these isoflavones.

Table 10

Isoflavone Content of Various Soy Products  $\mu\text{g/g}$  dry wgt.

	Diadzin	Genistein	Glycitein	Total
Raw soybean	455	484	69	1008
Toasted soybean	526	624	9	1159
Soy protein isolate	488	937	88	1513
Soy protein concentrate				
- water washed	623	1127	78	1828
- alcohol washed	29	49	0	78
Tofu (soy curd)*	146	162	29	337
Bean paste*	272	242	77	593
Soy flour*	226	840	88	1124

\* Taken from Wang and Murphy, J. Agric. Food Chem. (1994) 42/1666-1673.

## 5 Example 2

Raw soybeans were soaked in water for about 20 to 30 minutes and then drained prior to roasting. An oven was pre-heated to about 450°F. The drained, pre-soaked soybeans were then spread in a layer (one bean deep) on a screen which was placed in the pre-heated oven. The beans were roasted for about 2 minutes, and then were stirred (to prevent surface scorching). The roasting process was continued for a total of about 8 minutes in total, stirring the beans about every two minutes. The beans were removed from the oven when they had a light brown or tan color. The beans were found to be generally similar in taste and appearance to the soybeans roasted as described in Example 1, although some scorching was sometimes observed, and the beans roasted at lower temperature were found to be somewhat less stable in storage than the roasted beans of Example 1.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention.

20 The contents of all publications cited herein are hereby incorporated by reference in their entirety.

What is claimed is:

- 26 -

1. A method for roasting soybeans, comprising:  
exposing soybeans to hot air at a temperature in a range of about 570°F to  
about 630°F. for not more than about two minutes;  
such that the soybeans are roasted.
- 5 2. The method of claim 1, wherein the soybeans are exposed to hot air for not more  
than about one minute.
3. The method of claim 1, wherein the soybeans are whole soybeans.
- 10 4. The method of claim 3, wherein the soybeans are unhulled soybeans.
5. The method of claim 1, wherein the soybeans are not contacted with oil during  
the exposure to hot air.
- 15 6. The method of claim 1, wherein the soybeans are not soaked in water prior to the  
step of exposing the soybeans to hot air.
7. A soybean roasted by the method of claim 1.
- 20 8. A roasted soybean having a moisture content of between about 4% and about  
12%, an oil fat content of not more than about 25%, a light brown color, a crisp texture,  
and a nut-like flavor, and having substantially no beany flavor.
- 25 9. The roasted soybean of claim 8, further comprising an edible hull.
10. The roasted soybean of claim 8, further comprising at least about 50% of the  
isoflavones present in a raw soybean.
- 30 11. A food preparation comprising the soybean of claim 8.
12. The food preparation of claim 11, wherein the food preparation includes at least  
about 30% by weight of the soybean.

13. A method for treating a disease condition, comprising administering to a patient in need thereof an effective amount of a food preparation comprising at least two therapeutically-effective components, which therapeutically-effective components act synergistically to treat said disease condition, such that the disease condition is treated.
- 5 14. The method of claim 13, wherein the food preparation comprises a roasted soybean having a moisture content of between about 4% and about 12%, an oil fat content of not more than about 25%, a light brown color, a crisp texture, and a nut-like flavor, and having substantially no beany flavor.
- 10 15. The method of claim 14, wherein the disease condition is selected from the group consisting of cardiovascular disease, hypercholesterolemia, cancer, hypertension, and diabetes and post-menopausal conditions.
- 15 16. The method of claim 14, wherein the food preparation is substantially free of exogenous therapeutically-effective components.
17. The method of claim 14, wherein the therapeutically-effective components are classified as GRAS.
- 20 18. A synergistic composition comprising an effective amount of at least two cholesterol-lowering components selected from the group consisting of antioxidants, soy lecithin, soy fiber, and soy steryl glycosides.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/12699

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A23L1/20 A61K35/78

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 865 956 A (FUKUSHIMA DANJI ET AL) 11 February 1975 see column 4, line 43 - line 54 see example 2	1-13, 18
X	--- H.E. SNYDER, T.W. KWON: "Soybean Utilization" 1987, AVI, USA XP002044045 Pages 60-71, 187-195, 200-205, 208, 209, 221-223 see page 66 - page 69 see page 202 see page 208 - page 209 see page 221 - page 223 see page 222; table 7.3. --- -/--	8, 11, 12, 18

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*&\* document member of the same patent family

Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/12699

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 289 060 A (SOLNUTS BV) 2 November 1988 see example ---	8,11,12, 18
X	WO 96 10341 A (SCHOUTEN IND BV ;HAASTER JOSEPH NICOLAAS VAN (NL)) 11 April 1996 see page 2, line 10 - page 4, line 25 see example 2 ---	13-17
X	WO 95 08342 A (INPHARMA S A ;FESTOE NORBERTO (CH)) 30 March 1995 see page 1, line 15 - page 2, line 6 see page 4, line 9 - line 24 ---	13
X	WO 93 23069 A (KELLY GRAHAM EDMUND) 25 November 1993 see page 6, paragraph 2 see page 8, paragraph 2 - paragraph 5 see page 12, paragraph 4 - page 13, paragraph 1 see page 15, line 1 - line 4 see example 4 ---	13
X	US 5 498 631 A (GORBACH SHERWOOD L ET AL) 12 March 1996 see column 1, line 30 - column 2, line 3 ---	13,18
X	DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US AN 101:150395, YAMAGUCHI M.: "Limiting Amino Acids of Soybean Protein Isolate and their Supplementary Effects" XP002044046 see abstract & DAIZU TANPAKUSHITSU EIYO KENKYUKAI KAISHI, vol. 4, no. 1, 1983, pages 65-68, ---	13-18
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# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US 97/12699

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons.

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97 12699

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 13

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

In view of the large number of compositions which are theoretically defined by the expressions 'a food preparation comprising at least two therapeutically-effective components' in claim 13, the search has been restricted for economic reasons to:

- food compositions according to claims 7-12 (i.e. comprising a roasted soybean)
  - compositions according to claim 18
- (PCT Search Guidelines PCT/GL2, Chapter III, 2.1., 3.6. and 3.7. ).

Remark : Although claims 13-17 are directed to a method of treatment of the human body , the search has been carried out and based on the alleged effects of the composition.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/12699

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